MITA
MEDICAL IMAGING
& TECHNOLOGY ALLIANCE
A DIVISION OF NEMA

1300 North 17th Street ▪ Suite 1752
Arlington, Virginia 22209
Tel: 703.841.3200
Fax: 703.841.3392
www.medicalimaging.org

December 30, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2008-D-0525

Dear Sir/Madam:

The following are MITA's specific comments on Docket No. FDA-2008-D-0525, the draft guidance "*Guidance for Industry: New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products.*" These comments are intended to supplement our accompanying letter that sets forth our general comments. The line numbers indicated below correspond to the lines of text in the draft guidance. The draft guidance that contains these line numbers in the text is attached for your reference.

Specific Comments

Lines 47-50: We suggest that this section be clarified. The current statement could be interpreted two ways: (1) that drug or biological product application holders *should* (i.e., are routinely encouraged/expected to) submit an efficacy or labeling supplement to add labeling for a new indication approved/cleared under a device application, OR (2) if a drug or biological product application holder *wishes* to add labeling for a new indication approved/cleared under a device application, they would do this by submitting an efficacy or labeling supplement. It is currently unclear whether the current statement is meant to describe the regulatory pathway to be used as an option to drug application holders (as implied in the parallel section governing device applications in lines 51-53), or whether FDA intends that drug application holders are routinely encouraged/expected to update their labeling following approval/clearance of a related device application. Please clarify whether such supplements are expected and if so, in what time frame.

Lines 67-69: The definition of "Contrast indication" should be changed to read as follows: "A contrast indication is a statement in the indication or intended use of either an imaging drug or imaging device using an imaging drug or biological product, including radiopharmaceuticals."

Lines 160-161: The draft guidance states: "When an imaging drug is intended to be used with a legally marketed device, the labeling of the drug typically describes the approved imaging contrast indication(s) with specificity." Further clarity is needed for stakeholders to understand

the level of specificity (organ or tissue) that would constitute a new contrast indication for an already approved body region indication.

Lines 199-200: One of the stated intentions of the draft guidance is to promote "comparability in labeling format and content (to the extent permissible under the different regulatory authorities)," but the draft guidance does not otherwise address how the labeling of the drug and device should be made comparable in format or content. MITA believes that this provision is overly prescriptive, particularly with regard to FDA's preference for comparability of labeling content. Instead, industry would like to present to FDA for review and discussion its views on what would be appropriate with regard to labeling format and content.

Lines 206-216: The draft guidance explains that, in appropriate circumstances and with appropriate supporting data, the labeling of the imaging device could be expanded without requiring conforming changes to the drug labeling. FDA explains that "this may occur when the device technology does not alter the drug and when the drug use is *otherwise consistent* [emphasis added] with its approved labeling." Much of the applicability of this draft guidance is predicated on a clear understanding of what it means for the drug use to be "otherwise consistent" with its approved labeling. The single example provided in this section of the draft guidance (quantitative angiography) concerns a situation that appears to be completely consistent with the current use of the drug. We respectfully request that FDA provide additional examples to further elucidate these principles. We also suggest that FDA clarify what is meant in line 214 by a "new yet consistent contrast indication."

Similarly, later in that same paragraph, in explaining when a device submission alone should suffice, FDA notes that the "drug labeling does not need revision." The draft guidance should better define, and illustrate by way of examples, what it means for use of the drug to be "otherwise consistent" with its approved labeling, and when the "drug labeling does not need revision." It should also be clarified whether the drug labeling can be revised by cross-reference to the device approval/clearance if the drug sponsor should decide to do so.

Finally, it would also be helpful to have additional clarification on what it means for the device technology to "alter the drug." For example, in the past, manufacturers have discussed with FDA new applications of ultrasound imaging that require bursting of ultrasound microbubbles, which some might interpret to "alter the drug." Would this kind of ultrasound imaging not be amenable to the "device only" application strategy FDA outlines in this draft guidance, if all other conditions are met?

Lines 223-231: Similar to our comment for lines 206-216 above, the draft guidance should clarify what is meant for a contrast indication to be "consistent with the drug's approved indication."

Lines 234-242: The draft guidance provides the example of a drug reformulation change made to allow enhanced biodistribution to a new "area" (assumed region of the body) using the same imaging software. In this case, FDA recommends that an NDA/BLA supplement would be needed, and that a device application would not be necessary. Would the converse be true? If changes to imaging device software are made to allow better visualization of contrast in a new region of the body, would such use be considered "otherwise consistent," and therefore could be approved/cleared under a device application without the need for a drug application?

Footnote 8: MITA believes that a burden should not be imposed on the part of device manufacturers to seek clearance of the contrast agent used with the device or on cross approvals of both the drug and device labeling. Device manufacturers should need to be focused only on the product clearance of the device. MITA believes that there should be separate labeling for the drug and device, and device and drug labeling need not be identical.

Finally, while we recognize that the new drug product exclusivity provisions of the Act apply to drug and biological product applications, and not device submissions, we request that FDA clarify whether drug and biological product application holders who submit efficacy supplements for new contrast indications supported by cross-reference to approval/clearance of a new contrast indication in a device application, will each receive exclusivity for that indication, starting from the date of approval of the new indication for the drug.

Lines 258-263: Rather than introduce new terms or principles in this draft guidance, we recommend FDA clarify when a device submission is required to reflect an imaging drug modification by tying the trigger for a device submission to existing CDRH guidance, i.e., "Deciding When to Submit a 510(k) for a Change to an Existing Device" and the draft guidance "Modifications to Devices Subject to Premarket Approval – the PMA Supplement Decision Making Process."

Line 267: We suggest that FDA broaden its discussion of the kind of data that will be required to establish a new contrast indication. While we understand that "clinical trials" will be necessary in most cases, in appropriate cases it is possible that other data may be adequate. Language such as "clinical studies or other appropriate data" would cover this concern.

Lines 304-305: The draft guidance explains that clinical studies conducted by device developers wishing to add a new contrast indication should "proceed under the investigational device exemption (IDE) regulations *with a submission to CDRH*" [emphasis added]. Some imaging device investigations are considered "non-significant risk" (NSR). While these NSR studies are conducted under the IDE regulations and require IRB approval, they do not require IDE submission to CDRH. It would be helpful if FDA clarified the investigational submission requirements for NSR imaging device sponsors wishing to add a new contrast indication.

Line 351: Similar to our comment above regarding line 267, we recommend this section be written more generically in that some changes may not require full scale clinical trials.

Lines 362-363: Similar to our comments above regarding lines 267 and 351, we recommend replacing "trials" by "studies" here and where applicable throughout the document. Furthermore, one or more examples might help illustrate what FDA intends by lines 362-363. One example might be the recommendation for cardiac monitoring for possible arrhythmias during and immediately following the administration of ultrasound microbubble contrast agents.

Lines 402-416: While we understand FDA's rationale that some changes to 510(k)-cleared imaging devices to include new contrast indications may require premarket approval (PMA) applications, here, and in lines 44-46, we believe FDA should take a case-by-case approach in making this determination. Further, the approach should be based on the longstanding principles embodied in the Office of Device Evaluation's "Substantial Equivalence Decision-Making

Process" described in Blue Book Memorandum K86-3 and later codified into statute and regulations. While the draft guidance asserts that "the need for a PMA reflects the new type of safety and effectiveness questions that arise when the new imaging drug-device indication is added to the device submission, particularly in the absence of a concurrent NDA," according to FDA's longstanding substantial equivalence decision-making process, one must ask whether "new types of safety and effectiveness questions" are raised only if the device has different technological characteristics that could affect safety and effectiveness. In some cases, the device may not require changes in order to permit the new contrast indication, and therefore "new types of safety and effectiveness questions" do not play a role in the decision-making process. We believe a more appropriate mechanism to address this concern in the draft guidance is to note that, for 510(k)-cleared devices, new contrast indications will be assessed using the established substantial equivalence decision-making process, as required by statute, regulation and long-standing policy. The established substantial equivalence decision-making process provides considerable flexibility to permit FDA to direct contrast indications into either the PMA or 510(k) process, as appropriate, given the specific situation.

This section of the draft guidance also recommends that a PMA is necessary in certain situations, "particularly in the absence of a concurrent NDA." In the case where the same type of changes are being made but a concurrent NDA *is* being submitted, we request that the draft guidance clarify whether a PMA would still be necessary, or whether a 510(k) could then be submitted.

Lines 420-424: Please reference our comment relevant to lines 402-416 above, i.e., that "new types of safety and effectiveness questions" may not necessarily be part of the substantial equivalence decision making process for a 510(k)-cleared imaging device, depending on the changes necessary to affect the new contrast indication.

In addition, we believe the single example FDA cited as to when a 510(k) may be appropriate requires clarification. The draft guidance notes that a 510(k) "might be acceptable if the approved imaging drug and cleared imaging device are already indicated for the same or consistent contrast indication." If the imaging device is already indicated for the "same" contrast indication, why would any additional premarket approval/clearance (whether PMA or 510(k)) be necessary? Furthermore, as noted in other comments described above, FDA should clarify what it means for a new contrast indication to be "consistent" with that in an approved product.

Finally, while the draft guidance notes that a PMA may be needed particularly for new contrast indications within the categories of disease or pathology detection or assessment; functional, physiological or biochemical assessment; and diagnostic or therapeutic patient management, we note that the omission of structural assessment implies that structural claims may be more amenable to a 510(k) approach. It would be helpful if the draft guidance further clarified this point.

Lines 430-432: The draft guidance notes that "if FDA approves or clears a new contrast indication in a device submission, the NDA/BLA holder may submit a labeling supplement to add the indication to the imaging drug." We recommend that footnote 8 be clarified (see comment above) to make the document internally consistent. Further, based on the guiding principles described in the draft guidance, we recommend that the draft guidance clarify that the data necessary to support such a drug labeling supplement should be consistent with what was

required to support the device approval/clearance. When a device submission is being made, data should be consistent with the device submission and not the drug submission.

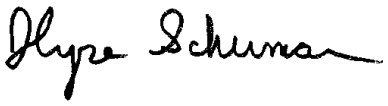
Lines 436-437: The draft guidance recommends that the "holder of an approved device submission that includes a new contrast indication should monitor changes to the marketed drug labeling *as well as other changes to the drug*" [emphasis added]. This sentence should be removed. Device manufacturers do not have the surveillance resources to monitor changes to the marketed drug labeling or other changes to the drug and should not be required to do so. MITA believes instead that the drug manufacturers should monitor any changes to the drug labeling, or other changes, and notify device manufacturers accordingly.

Lines 439-442: The draft guidance states that "Further to enhance adverse event reporting, FDA expects that the application holder adding the new contrast indication should submit to FDA any reports of adverse events related to the indication *in its labeling*" [emphasis added]. We recommend that the draft guidance clarify that such reports would only need to be submitted under the manufacturer's obligations under the Medical Device Reporting (MDR) regulation, 21 CFR 803. Further, we recommend that the wording be clarified so as not to imply that the adverse events should actually be submitted (or added to) the device labeling, as could be construed from the sentence as currently worded. The words *"in its labeling"* should be removed, which would provide clarity without any loss of meaning from the remainder of the sentence.

Line 468: FDA previously clarified (lines 282-283) that most concomitant uses of imaging devices and contrast agents do not represent a combination product. Line 468, however, uses the term "combination product," apparently inadvertently. We recommend that the final clause "for the combination product" be removed without any loss of meaning from the remainder of the sentence.

If you have any questions, or need further information, please do not hesitate to contact Richard Eaton of my staff at (703) 841-3248 or at reaton@medicalimaging.org.

Sincerely,



Ilyse Schuman
Vice President, National Electrical Manufacturers Association (NEMA)
Managing Director, Medical Imaging & Technology Alliance (MITA)

Attachments